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COMPLETE SPECIFICATION

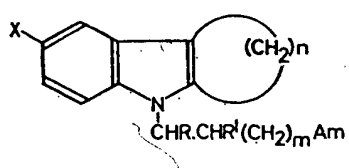
Improvements in and relating to N-Substituted 2,3-Polymethyleneindoles

We, AMERICAN HOME PRODUCTS CORPORATION, a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 685, Third Avenue, New York, 17, New York, United States of America, (assignee of LEONARD MARCUS RICE and MEIER EZRA FREED), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel compounds possessing valuable pharmacological properties affecting the central nervous system, and to methods of preparing these compounds. The compounds of this invention are of value as antidepressants, as inhibitors of appetite (especially in combination with amphetamine or other phenethylamine derivatives), and as antihistamines. Additionally, they have useful ataractic or tranquilizing action, and some exhibit analgesic action.

In the following description and claims, the term "lower alkyl" is to be construed as meaning alkyl groups having from 1 to 6 carbon atoms.

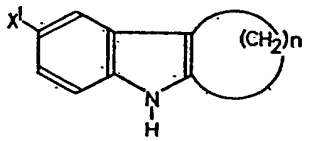
The pharmacologically valuable compounds of this invention are N-substituted 2,3-polymethyleneindoles and may be represented by the following formula



where X is hydrogen, halogen, methyl, nitro, or amino, m is 0 or an integer of from 1 to 4, preferably 0 or 1, n is an integer of from 5 to 13 inclusive, preferably from 5 to 8, R is hydrogen or phenyl, R^1 is hydrogen or methyl, and Am is amino, lower alkylamino, di(lower) alkylamino, hydroxy lower alkylamino, di(hydroxy lower alkyl)amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N-hydroxy lower alkyl piperazino. Thus, for example Am may represent the unsubstituted amino radical, a methylamino, ethylamino, propylamino, butylamino, hexylamino, hydroxyethylamino, hydroxypropylamino, dimethylamino, diethylamino, dibutylamino, methylhexylamino, diethanolamino, pyrrolidino, piperidino, morpholino, or piperazino, N-(lower alkyl)piperazino, and N-(lower hydroxyalkyl)piperazino.

The above defined compounds, it will be noted, are indoles, and are preferably administered in the form of their salts with pharmaceutically acceptable acids which may include acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, citric, malic, maleic, propionic, acetic, and fumaric.

The compounds of this invention may be prepared by any of several relatively simple procedures from 2,3-polymethyleneindoles having the formula



where X^1 represents hydrogen, halogen, nitro, or methyl, and n is an integer of from 5 to 13, inclusive.

Compounds of this invention may be pre-

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pared by a process which includes as a first step treating such a 2,3-polymethyleneindole with a reagent capable of substituting on the indole nitrogen atom a substituent having the formula

$$—W—CHR^1(CH_2)_mY$$

where W is methylene, benzylidene, or —C: O.O—, R^1 is hydrogen or methyl, m is 0 or an integer of from 1 to 4, preferably 0 or 1, and Y is a carboxylic acid radical, a carboxylic ester radical, a nitrile radical, an hydroxy radical, bromine, chlorine, iodine, an alkylsulfonyloxy radical, an arylsulfonoxy radical, or amino, lower alkylamino, di(hydroxy amino, hydroxy(lower)alkylamino, di(hydroxy lower alkyl)amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N-hydroxy lower alkyl piperazino. For example, the sodio derivative of the 2,3-polymethyleneindole (prepared by treating a dimethylformamide solution of a 2,3-polymethyleneindole with a dimethylformamide suspension of sodium hydride) may be warmed with a dialkylaminoalkyl halide, alkylsulfonate, or arylsulfonate, preferably a chloride or bromide, to yield an N-(dialkylaminoalkyl) 2,3-polymethyleneindole of this invention. (Obviously, if a 1-phenyldialkylaminoalkyl halide is employed, the group substituted on the indole nitrogen atom will be one in which W is benzylidene, and the product will be an N - (dialkylaminophenylalkyl) - 2,3 - polymethyleneindole). As another example, a 2,3-polymethyleneindole may be treated with a dialkylaminoalkyl chloroformate, such as for example, 2-dimethylaminoethyl chloroformate to yield a 2,3-polymethyleneindole-N-carboxylic acid 2-dimethylaminoethyl ester; heating this urethane-type compound results in evolution of carbon dioxide and the formation of an N - (2 - dimethylaminoethyl) - 2,3-polymethyleneindole of this invention.

Where W is a —COO group it is necessary to heat the compound prior to treatment of the Y radicals.

If instead of substituting a

$$—W—CHR^1(CH_2)_mY$$

group in which Y is amino, lower alkylamino, di(lower)alkylamino, hydroxy(lower)alkylamino, di(hydroxy lower alkyl)amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N - hydroxy lower alkyl piperazino, as in the above, one introduces such a substituent in which Y is a carboxylic acid radical, a carboxylic ester radical, a nitrile radical, an hydroxy radical, a bromine, chlorine or iodine atom, or an alkyl- or aryl sulfonoxy radical, one may then proceed by amidating in the case where Y is halogen alkyl sulfonoxy or arylsulfonoxy; reducing followed by halogenation and amidation or amidating and reducing where Y is a carboxylic acid radical or a carboxylic acid ester; halogenating and amidating where Y is hydroxyl, and where Y is nitrile reducing or forming the corresponding carboalkoxyalkyl compound and then reducing halogenating and amidating or amidating and reducing to replace these by or convert them into suitable amino radicals. Thus, an N - (haloalkyl) - 2,3 - polymethyleneindole may be readily converted to an N-(aminoalkyl) - 2,3 - polymethyleneindole by heating with ammonia or a suitable primary or secondary amine, preferably in a suitable neutral inert solvent. If one of these substituted 2,3-polymethyleneindoles in which Y is a hydroxyl group is treated with thionyl chloride or concentrated hydrobromic acid, it may be converted to the corresponding compound in which Y is chlorine or bromine, and these intermediates may be reacted with ammonia or a primary or secondary amine, as above. Likewise, a polymethyleneindole intermediate in which Y is a carboxylic acid radical or a carboxylic ester radical may be reduced, as with lithium aluminum hydride, to a polymethyleneindole intermediate in which the substituent tail is terminated by a $—CH_2OH$ radical; as outlined above, this OH may be replaced by halogen which may then be replaced by amino to yield a compound of this invention.

Acrylic and methacrylic esters, such as the methyl and ethyl esters are convenient reagents for preparation of N - (carboalkoxyalkyl) - 2,3-polymethyleneindoles. Acrylonitrile and methacrylonitrile are similarly useful in the preparation of N - (cyanoalkyl) - 2,3 - polymethyleneindoles such as N - (2 - cyanoethyl)-2,3 - polymethyleneindoles and N - (2 - cyanopropyl) - 2,3 - polymethyleneindoles. Acrylic and methacrylic esters and nitriles readily add 2,3-polymethyleneindoles under the influence of basic catalysts, such as tetraalkyl ammonium hydroxides.

The N - (2 - cyanoethyl) - 2,3 - polymethyleneindoles and N - (2 - cyanopropyl)-2,3-polymethyleneindoles so formed may be converted by any of several routes to compounds of this invention. By catalytic or chemical reduction they may be converted to N - (2 - aminoalkyl) - 2,3 - polymethyleneindoles of this invention. By treatment with an anhydrous alkanol and an anhydrous hydrogen halide, they may be converted via the iminoethers to N - (2 - carboalkoxyalkyl)-2,3-polymethyleneindoles, which by methods outlined above may be converted to compounds of this invention.

A particularly valuable method of producing N-(secondary aminoalkyl)-2,3-polymethyleneindoles comprises treating an N-(carboalkoxyalkyl)-2,3-polymethyleneindole with a primary amine, such as, for example, methylamine, to produce an N - (carboalkamidoalkyl) - 2,3-

polymethyleneindole which may be readily reduced, as with lithium aluminum hydride, to an N - (alkylaminoalkyl) - 2,3 - polymethyleneindole.

When the synthetic route has led to an N-(primary aminoalkyl) - 2,3 - polymethyleneindole or an N-(secondary aminoalkyl)-2,3-polymethyleneindole, these can, if desired, be alkylated or hydroxyalkylated to replace the hydrogen atom or atoms on the amino nitrogen by alkyl or hydroxyalkyl radicals. Suitable alkylating agents include methyl iodide, diethyl sulfate, and butyl bromide; suitable hydroxyalkylating agents include ethylene oxide, propylene chlorohydrin, and ethylene carbonate.

When the 2,3-polymethyleneindole starting material is substituted at the 5-position by nitro and it is desired to have a 5-amino-N-(aminoalkyl)-2,3-polymethyleneindole, reduction of the 5-nitro group is best carried out as a final step.

The new pharmacologically active compounds of this invention may be administered parenterally or orally after being combined with suitable solvents, carriers, buffers, fillers, etc.

The preparation of the compounds of this invention is illustrated by but in no manner limited to the following examples:

EXAMPLE 1

1-(3-Dimethylaminopropyl)-2,3-Hexamethyleneindole.

3-Dimethylaminopropylchloride (12.1 grams, 0.1 mole) is added to a well-stirred suspension of 1-sodio-2,3-hexamethyleneindole (from 19.5 grams, 0.1 mole of 2,3-hexamethyleneindole and 6 grams, 0.1 mole, of 48% sodium hydride dispersion) in 150 cc of dimethylformamide. After 6 hours, the reaction mixture is poured into 500 cc of ice-water and the oil layer extracted into ether. The ether extract is washed with water and the aqueous fraction discarded. The ether solution is then extracted with *N* HCl until acidic, then with water. The aqueous acid solution is washed with ether. After basifying the aqueous solution, the product is extracted into ether, and the ether solution washed with water and dried. Concentration yields an orange oil. This is dissolved in absolute ethanol, and dry HCl is added until strongly acidic. On addition of ether the product hydrochloride crystallizes out. After recrystallization from ethanol-ethyl acetate-ether it melts at 146—147°C. Yield: 14.9 grams (46.7%).

Analysis:	N	Cl
Calculated for $C_{19}H_{29}N_2Cl$	8.7	11.06
Found	8.59	10.90

In a similar manner, 1(3-dimethylamino-isobutyl)-2,3-hexamethyleneindole may be prepared from the sodio derivative of 2,3-hexamethyleneindole and 3-dimethylamino-isobutyl chloride.

EXAMPLE 2

1-(3-Aminopropyl)-2,3-Pentamethyleneindole.

(a) Acrylonitrile, 11 grams (0.2 mole), is added slowly with cooling to a solution of 2,3-pentamethyleneindole, 37 grams (0.2 mole), and 4 ml. of trimethylbenzylammonium methoxide (40% in methanol) in 100 ml. of benzene. The reaction temperature reaches 50° and then drops slowly. After stirring for an additional hour, 5 ml. of concentrated hydrochloric acid is added. The benzene solution is washed well with water, and then dried over sodium sulfate. The solution is concentrated and the residue crystallized from acetone-methanol. Yield of 1 -(2 - cyanoethyl) - 2,3-pentamethyleneindole: 27 grams (56.6%), m.p.: 95—96°C.

Analysis:	C	H	N
Calculated for $C_{16}H_{18}N_2$	80.50	7.60	11.78
Found	80.41	7.64	11.76

(b) A solution of 24 grams (0.1 mole) of 1 - (2 - cyanoethyl) - 2,3 - pentamethyleneindole in 100 ml. of dry benzene is added slowly to a stirred suspension of 6 grams of lithium aluminum hydride (0.15 mole) in 500 ml. of dry ether. The mixture is heated to reflux and stirred overnight. Water, 30 ml., is added slowly with cooling. One hour after addition is completed the mixture is filtered and the filtercake washed well with ether. After removing the solvent the residue is distilled. This yields 20 grams (81.5%) 1-(3-aminopropyl) - 2,3 - pentamethyleneindole, b.p.: 190—192°/0.7 mm.

Analysis:	C	H	N
Calculated for $C_{16}H_{22}N_2$	79.25	9.22	11.58
Found	78.99	9.18	11.61

A sample is converted to the hydrochloride salt which is recrystallized from methanol-acetone: m.p. 271—272°.

Analysis:	N	Cl
Calculated for $C_{16}H_{23}ClN_2$	10.05	12.72
Found	10.15	12.75

EXAMPLE 3

1-(3-Di-[2-Hydroxyethyl]Aminopropyl)-2,3-Hexamethyleneindole.

To a solution of 11.5 grams (0.045 moles) 1 - (3 - aminopropyl) - 2,3 - hexamethyleneindole in 50 ml. of methanol is slowly added 4.4 grams (0.1 mole) of ethylene oxide. After standing 2 days the solvent is evaporated off and the residue distilled. This yields 12 grams (77.5%) of product; b.p.: 245—50°/.001 mm.

Analysis:	C	H	N
Calculated for $C_{21}H_{32}N_2O_2$	73.20	9.36	8.13
Found	72.98	9.62	7.92

EXAMPLE 4

1-(2-Carboethoxyethyl)-2,3-Pentamethyleneindole.

(a) Forty grams (0.17 mole) of 1-(2-cyanoethyl)-2,3-pentamethyleneindole, prepared as described in Example 2, is dissolved in 300 ml. of absolute ethanol. The resulting solution is saturated with dry hydrogen chloride, 2 ml. of water is added, and the mixture boiled under reflux for two hours and then cooled to room temperature. Ammonium chloride which separates is filtered off and the filtrate concentrated *in vacuo*. The residue is taken up in ether, water-washed, and dried. The solvent is then evaporated and the product distilled. The yield is 31 grams of material boiling between 220 and 225 C at 0.05 mm. Hg.

Analysis:			
Calculated for $C_{18}H_{23}NO_2$	75.75	8.12	4.91
Found	75.56	8.26	4.79

1-(3-Hydroxypropyl)-2,3-Pentamethyleneindole.

(b) A solution of 1 - (2 - carboethoxyethyl)-2,3 - pentamethyleneindole (31 grams, (0.11 mole), in 200 cc. dry ether is added slowly to a stirred suspension of 3 grams (0.05 mole) of lithium aluminum hydride in 200 cc. dry ether. After 4 hours refluxing the reaction mixture is cooled, 12 cc. of water is added dropwise, and then 50 cc. isopropanol. The suspension is filtered, the filtercake washed well with isopropanol, the combined filtrates concentrated and the residue distilled, b.pt.: 210—215°/.05 mm. Yield 22 grams (82.3%).

Analysis:	C	H
Calculated for $C_{16}H_{21}NO$	78.90	8.70
Found	78.84	8.40

1-(3-Bromopropyl)-2,3-Pentamethyleneindole.

(c) 5 grams (0.02 mole) of 1-(3-hydroxypropyl) - 2,3 - pentamethyleneindole, 10 cc. 48% aqueous hydrogen bromide, and 2 cc. of concentrated sulfuric acid are placed in a 25 cc. round-bottomed flask and refluxed 1½ hours. The mixture is cooled, poured onto ice, and extracted with ether. The extract is washed successively with water, sodium bicarbonate solution, and water, and then dried over sodium sulfate. Solids are filtered off and the filtrate concentrated. The residue is distilled under vacuum yielding 2.8 grams product, b.pt.: 185—190°/0.05 mm.

Analysis:	C	H	N	Br
Calculated for $C_{16}H_{20}NBr$	62.75	6.58	4.57	26.08
Found	63.88	6.77	4.49	25.92

1-(3-[4-(2-Hydroxyethyl)Piperazino]Propyl-2,3-Pentamethyleneindole.

(d) Eight grams (0.026 moles) 1-(3-bromopropyl) - 2,3 - pentamethyleneindole and 4-(2 - hydroxyethyl)piperazine (3.9 grams, 0.03 mole) in 100 cc. xylene are heated under reflux for 24 hours. After cooling, the mixture is washed with aqueous potassium carbonate, then with water. The organic layer is dried over magnesium sulfate, and after filtration the solution is diluted with ether and dry hydrogen chloride is added. A precipitate is separated and twice crystallized from alcohol. m.p. 209—210°.

Analysis:	N	Cl
Calculated for $C_{22}H_{35}N_3Cl_2O$	9.82	16.55
Found	9.52	16.70

EXAMPLE 5

1-(3-Methylaminopropyl)-2,3-Hexamethyleneindole.

(a) 1-(2 - Carbomethoxyethyl) - 2,3 - hexamethyleneindole is prepared from 75.8 g. of 1 - (2 - cyanoethyl) - 2,3 - hexamethyleneindole (prepared by the general procedure of Example 2) by following the general procedure of Example 4 (a), using 1250 ml. of methanol and 5 ml. of water. The product has a melting point of 62—64°.

Analysis:	C	H	N
Calculated for $C_{18}H_{23}O_2N$	75.75	8.12	4.91
Found	75.49	8.10	4.94

(b) 1 - (2 - Carbomethamidoethyl) - 2,3-hexamethyleneindole is prepared by dissolving 10 grams of 1 - (2 - carbomethoxyethyl) - 2,3-hexamethyleneindole (prepared as in part (a) of this example) in 50 ml. of methanol saturated at 0°C with methyl amine. After standing at room temperature for 48 hours, the solvent is evaporated by heating on the steam bath. Recrystallization from methanol gives a colorless product melting at 115—116°.

Analysis:	C	H	N
Calculated for $C_{18}H_{24}N_2O$	76.05	8.50	9.86
Found	75.83	8.50	9.84

(c) Eleven grams of the product of part (b) of this example is dissolved in about 500 ml. of benzene and then added to a solution of 10 grams of lithium aluminum hydride in 1000 ml. of anhydrous ether. After decomposition of the complex by addition of about 25 ml. of water, the mixture is filtered, the filtrate dried, and the solvent evaporated off. The residue is distilled to yield 1 -(3 - methylaminopropyl)-2,3-hexamethyleneindole, b.pt.: 160—170° at 0.1 mm. Hg. A portion of the base is converted to the hydrochloride salt, m.p. 180—181°.

Analysis:	C	H	N
Base			
Calculated for $C_{18}H_{26}N_2$	79.95	9.69	10.36
Found	79.83	9.82	10.25
Hydrochloride			
Calculated for $C_{18}H_{27}N_2Cl$	70.45	8.87	9.13
Found	70.76	9.00	9.41

EXAMPLE 6

1-(3-Dimethylominapropyl)-2:3-Pentamethyleneindole.

1 - (3 - Dimethylaminopropyl) - 2:3-pentamethyleneindole is prepared by heating the 3-dimethylaminopropyl ester of 2:3 - pentamethyleneindole - 1 - carboxylic acid, dissolved in *o*-dichlorobenzene till the evolution of carbon dioxide begins and continuing to heat until it ceases. The product is isolated and purified by vacuum distillation and may be converted to a salt such as the hydrochloride in the usual way.

The required starting material for this preparation may be obtained by heating together 2:3 - pentamethyleneindole (18.5 grams, 0.1 mole) and a toluene solution of phosgene (10 grams, 0.1 mole). The resulting 1-carbonyl chloride is then reacted with 3-dimethylaminopropinol (20 g., 0.2 mole) to give the required 3-dimethylaminopropyl ester of 1,3-pentamethyleneindole-1-carboxylate.

EXAMPLE 7

1-(3-Methylbutylaminopropyl)-2:3-Pentamethyleneindole.

1 - (3 - [Methylbutylamino]propyl) - 2:3-pentamethyleneindole is prepared by the addition of a solution of butyl bromide (13.7 grams, 0.1 mole) in xylene to a stirred and refluxing solution of 1 - (3 - methylaminopropyl)-2:3-pentamethyleneindole in xylene in the presence of excess powdered anhydrous potassium carbonate. After refluxing for 8—12 hours, the reaction mixture is cooled, filtered free of inorganic salts and the product isolated in the usual manner. Purification is accomplished by vacuum distillation or by conversion to a salt such as the hydrochloride or fumarate.

EXAMPLE 8

1-(2-Dimethylaminopropyl)-2,3-Pentamethyleneindole.

18.5 grams (0.1 mole) of 2.3 - pentamethyleneindole and 6 grams sodium hydride dispersion (48%, 0.12 mole) in 100 cc of dimethylformamide is stirred and warmed to 40°C. To this is added 12.1 grams (0.1 mole) of dimethylaminoisopropyl chloride and the reaction mixture is stirred and warmed (40°C) for 6 hours. The suspension is poured into ice-water (250 cc) and acidified with concentrated hydrochloric acid. The hydrochloride product crystallizes from the solution, is separated by filtration, and recrystallized from absolute ethanol, m.pt.: 189—190°C. Yield: 15.5 grams (50.5%).

Analysis:	N	Cl
Calculated for $C_{18}H_{27}ClN_2$	9.13	11.57
Found:	9.13	11.53

EXAMPLE 9

1-(2-Piperidinoethyl)-2,3-Pentamethyleneindole.

A solution of 18 grams (0.1 mole) 2,3-pentamethyleneindole in 50 ml. of dimethylformamide is added slowly to 6 grams of 48% sodium hydride dispersion suspended in 50 ml. of the same solvent. This is stirred at 30—35°C. until the evolution of hydrogen ceases. To the stirred suspension is added 14.7 grams (0.1 mole) of freshly distilled 1-(2-chloroethyl)piperidine. After 16 hours the contents of the flask are poured into 300 cc. of ice-water and acidified with concentrated hydrochloric acid. The solution is then extracted well with ether to remove non-basic components. The aqueous acid solution is then made alkaline with 40% sodium hydroxide and the oil which separates extracted into ether. The ether solution is then washed with saturated salt solution and dried over sodium sulfate. The solvent is removed and the residual oil dissolved in 50 cc. of ethanol. Dry hydrogen chloride is bubbled through the solution until acidic. Acetone is then added until crystallization occurs. The product is filtered off, washed with ethanol-acetone, then with acetone and dried at 80°C./0.2 mm. The hydrochloride salt has m.p. 209—210°. Yield: 15.8 grams (48.3%).

Analysis:	N	Cl
Calculated for $C_{20}H_{29}ClN_2$	8.44	10.66
Found:	8.43	10.42

EXAMPLE 10

1-(2-Morpholinoethyl)-2,3-Pentamethyleneindole.

A solution of 2,3-pentamethyleneindole (18.53 grams, 0.1 mole) in 100 ml. of dimethylformamide is added slowly to a well-stirred suspension of sodium hydride (6 grams, 0.1 mole) dispersion (48%) in 50 ml. of the same solvent. The temperature is slowly elevated by heating to 30—35° until hydrogen is no longer evolved. Freshly distilled 1 - (2 - chloroethyl) morpholine (14.9 grams, 0.1 mole) is then added drop-wise and the mixture stirred and heated to 50° for 6 hours. The reaction is quenched by pouring into 300 ml of ice-water. Concentrated hydrochloric acid is added until the mixture is acidic (15—20 ml.) and it is then extracted several times with ether. The aqueous layer is separated, and on standing the hydrochloride salt precipitates. The precipitate is collected on a funnel, washed with cold water, and dried. The salt is recrystallized from dilute hydrochloric acid. Yield: 24 grams (71.6%). m.pt: 181—182°.

Analysis:	N	Cl
Calculated for $C_{19}H_{27}ClN_2O$	8.37	10.58
Found	8.35	10.45

EXAMPLE 11

1-(2-Pyrrolidinoethyl)-2,3-Pentamethyleneindole.

A solution of 2,3-pentamethyleneindole (18.53 grams, 0.1 mole) in 100 ml. of dimethylformamide is added slowly to a well-stirred suspension of sodium hydride (6 grams, 0.12 mole) dispersion (48%) in 50 ml. of the same solvent. The temperature is slowly elevated by heating to 30—35° until hydrogen is no longer evolved. Freshly distilled 1 - (2 - chloroethyl) pyrrolidine (13.5 grams, 0.1 mole) is then added drop-wise and the mixture stirred and heated to 50° for 6 hours. The reaction is quenched by pouring into 300 ml. of ice-water. Concentrated hydrochloric acid is added until a nearly clear solution results (15—20 ml.) and this is extracted several times with ether. The aqueous layer is made strongly alkaline and the product taken up in ether. The ethereal solution is washed with a saturated aqueous solution of sodium chloride, dried, and the solvent removed under reduced pressure. Distillation of the residue yields 9 grams of base, b.p.: 193—6/.2 mm. The product is dissolved in 50 ml. of acetone and converted to an acid addition salt by addition to a hot solution of fumaric acid in 250 ml. of acetone. Yield: 13 grams (32.6%) m.pt.: 244—245°.

Analysis:	C	H	N
Calculated for $C_{23}H_{30}N_2O_4$	69.30	7.55	7.03
Found	69.20	7.41	7.15

EXAMPLE 12

1-(3-Dimethylaminopropyl)-2,3-Pentamethylene-5-Fluoroindole Hydrochloride.

This is prepared in the manner of Example 8 using 10.15 grams (0.05 mole) of 2,3-pentamethylene-5-fluoroindole, 3 grams sodium hydride (48%) and 6.08 grams of 3-dimethylaminopropylchloride in 75 cc. of dimethylformamide. The product (base) has b.pt.: 178—180°/.3 mm.: product (hydrochloride) has m.p.: 177—178°.

Analysis:	C	H	N
Calculated for $C_{18}H_{25}N_2F$	74.95	8.73	9.70
(Base)	74.75	8.76	9.72
Found	N	Cl	
Calculated for $C_{18}H_{26}N_2FCl$			
(Hydrochloride)	8.64	10.92	
Found	8.65	10.92	

The 2,3-pentamethylene-5-fluoroindole used as starting material in the example is prepared from *p*-fluorophenylhydrazine and cycloheptanone according to the procedure outlined in the second paragraph of Example 13. It melts at 114—115°C.

	C	H	N
Calculated for $C_{13}H_{14}FN$	76.80	6.96	6.90
Found	76.80	7.02	7.06

EXAMPLE 13

1-(3-Dimethylaminopropyl)-2,3-Pentamethylene-5-Chloroindole.

This is prepared as per Example 8, using 11 grams (0.05 mole) of 2,3-pentamethylene-5-chloroindole, 3 grams sodium hydride (48%) and 6.08 grams 3 - dimethylaminopropylchloride. The product (base) has a b.p. of 185—188°/.05 mm . yield: 9.5 grams (62.5%). The fumaric acid salt has m.p. 141—142°.

Analysis:	C	H	N
Calculated for $C_{18}H_{25}N_2Cl$			
(Base)	70.80	8.26	9.18
Found	70.88	7.94	9.17
Calculated for $C_{22}H_{29}O_4N_2Cl$			
(Fumarate)	62.80	6.94	6.67
Found	62.69	6.82	6.61

To prepare the 2,3-pentamethylene-5-chloroindole employed as starting material in the preparation, 44 g. of *p*-chlorophenylhydrazine (0.31 mole) is added to 34 g. (0.31 mole) of cycloheptanone in 250 ml. of glacial acetic acid, and the mixture is heated under reflux for two hours and then cooled. The crystalline product is filtered off and recrystallized from methanol. The 2,3-pentamethylene-5-chloroindole melts at 131—132°C.

Analysis:	Cl	N
Calculated for $C_{13}H_{14}ClN$	16.15	6.38
Found	16.05	6.10

EXAMPLE 14

1-(2-Dimethylaminoethyl)-2,3-Hexamethyleneindole.

This is prepared in the same manner as Example 1, using 2,3-hexamethyleneindole, 9.96 grams: 3.0 grams sodium hydride (48%): and 5.38 grams beta-dimethylaminoethylchloride.

The product base has b.pt.: 180—183°/.3: Fumarate m.pt. 198.5—201°.

Analysis:	C	H	N
Calculated for $C_{18}H_{26}N_2$			
(base)	79.95	9.69	10.36
Found	79.85	9.46	10.34
Calculated for $C_{22}H_{30}N_2O_4$			
(Fumarate)	68.36	7.82	7.25
Found	68.32	8.04	7.28

EXAMPLE 15

1-(3-Dimethylaminopropyl)-2,3-Tridecamethyleneindole.

This is prepared essentially according to Example 8 from 2,3-tridecamethyleneindole (8.93 g., 0.03M) sodium hydride (1.8 g of 48% dispersion, 0.033 M), 3-dimethylaminopropylchloride (3.7 g 0.03 M) in dimethylformamide (65 ml.). Fumarate m.p. 147.5—149°C.

Analysis:	C	H	N
Calculated for $C_{30}H_{46}N_2O_4$	72.25	9.30	5.62
Found	72.11	9.38	5.71

EXAMPLE 16

1-(1-Phenyl-2-Dimethylaminoethyl)-2,3-Pentamethyleneindole.

This is prepared essentially according to Example 8 from 2,3-pentamethyleneindole (9.25 g., 0.05 M), sodium hydride (3.0 g. of 48% dispersion, 0.055 M) N,N-dimethyl-2-phenyl - 2 - chloroethylamine (9.20 g., 0.05 M) and dimethylformamide. Product m.p. 120—122° C.

Analysis:

	C	H	N
Calculated for $C_{23}H_{28}N_2$	83.08	8.49	8.43
Found	82.84	8.55	8.23

Fumarate: m.p. 195—197°C.

Analysis:

	C	H	N
Calculated for $C_{27}H_{32}N_2O_4$	72.27	7.19	6.25
Found	72.27	7.20	6.18

EXAMPLE 17

1-(3-[4-Methyl]Piperazinopropyl)-2,3-Pentamethyleneindole.

This is prepared essentially according to Example 8 from 2,3 - pentamethyleneindole (5.12 g., 0.0276 M), sodium hydride (1.66 g. of 48% dispersion, 0.0304 M), 1-methyl-4-(3-chloropropyl) piperazine (4.90 g., 0.0276 M) and dimethylformamide (50 ml.). Difumarate m.p. 217.5—218.5°C.

Analysis:

	C	H	N
Calculated for $C_{29}H_{39}N_3O_8$	62.46	7.05	7.54
Found	62.41	7.33	7.47

EXAMPLE 18

1-(3-Dimethylaminopropyl-2,3-Pentamethylene-5-Nitroindole.

This is prepared essentially as in Example 8 from 2,3 - pentamethylene - 5 - nitroindole (4.6 g., 0.02 M), sodium hydride (1.2 g. of 48% dispersion), 3-dimethylaminopropyl-chloride (2.5 g., 0.02 M) and dimethyl-formamide (50 ml.). Product m.p. 77.5—80°C.

Analysis:

	C	H	N
Calculated for $C_{18}H_{25}N_3O_2$	68.54	7.99	13.32
Found	68.70	8.09	13.12

Fumarate m.p. 178—180°C.

Analysis:

	N
Calculated for $C_{22}H_{29}N_3O_6$	9.74
Found	9.92

Hydrochloride m.p. 220—223°C.

Analysis:

	C	H	N	Cl
Calculated for $C_{18}H_{26}ClN_3O_2$	61.44	7.45	11.94	10.08
Found	61.26	7.49	12.04	10.04

The 2,3-pentamethylene-5-nitroindole employed as starting material in this example is prepared by refluxing for one hour a mixture of 51.1 g. of *p*-nitrophenylhydrazine, 37.5 g. of cycloheptanone and 900 ml. of absolute ethanol. On cooling, cycloheptanone *p*-nitrophenylhydrazone crystallizes and is filtered off and dried m.p. 142—143°C. This is cyclized by refluxing for one hour with four times its weight of glacial acetic acid saturated with dry hydrogen chloride. The cyclized product crystallizes on cooling, and is recrystallized from methanol, m.p. 164—165°C.

Analysis:

	C	H	N
Calculated for $C_{13}H_{14}N_2O_2$	67.81	6.13	12.17
Found:	67.72	6.24	12.15

EXAMPLE 19

1-(3-Dimethylaminopropyl)-2,3-Pentamethylene-5-Aminoindole.

1 - (3 - Dimethylaminopropyl) - 2,3 - pentamethylene-5-nitroindole fumarate (5.4 g., 0.01 M) is dissolved in 100 ml. of methanol and hydrogenated over 100 mgs. of PtO_2 at 45 psi and 25°C. When hydrogen uptake ceases (after 4 hours) the catalyst is filtered off and the solvent removed under vacuum. The residue is taken up in water, basified with 10% sodium hydroxide and extracted into ether. The ether layer is water-washed and dried; after filtering the filtrate is treated with dry hydrogen chloride. The dark gummy precipitate is washed by decantation with ether and then crystallized from isopropyl alcohol. m.pt.: 260—261°.

Analysis:

	N	Cl
Calculated for $C_{18}H_{27}N_3.2HCl$	11.73	19.78
Found	11.70	19.50

EXAMPLE 20

1-(3-Piperazinopropyl)-2,3-Pentamethylene-indole.

This is prepared essentially according to Example No. 8 from 2,3-pentamethyleneindole (5.56 g., 0.03 M), sodium hydride (1.8 g. 0.033 M of 48% dispersion) and a benzene solution of N - (3 - chloropropyl) - piperazine (obtained from 7.78 g. of hydrochloride, 0.033 M in 50 ml. dimethylformamide. Difumarate m.pt. 172—174°C (dec.).

Analysis:

	C	H	N
Calculated for $C_{28}H_{37}N_3O_8$	61.86	6.86	7.73
Found	61.73	6.96	7.98

EXAMPLE 21

1-(3-Dimethylaminopropyl)-2,3-Penta-methylene-5-Methylindole.

This is prepared by the procedure of Example No. 8 substituting 2,3-penta-methylene-5-methylindole for the 2,3-penta-methyleneindole employed in Example 8. The product is isolated and crystallized as the fumaric acid salt, m.p. 141.5—145°C.

Analysis:

	C	H	N
Calculated for $C_{23}H_{32}O_4N_2$:	68.97	8.05	7.00
Found	68.75	8.01	6.96

The 2,3 - pentamethylene - 5 - methylindole employed as starting material in this example is prepared from cycloheptanone and *p*-methylphenyl-hydrazine by the process outlined in the second paragraph of Example 13. m.p., 123—127°C.

EXAMPLE 22

1-(3-Dimethylaminopropyl)-2,3-Octa-methyleneindole.

This is prepared essentially according to Example No. 1 from 2,3-octamethyleneindole (5.68 g., 0.025 M), gamma-dimethylamino-propyl chloride (3.25 g., 0.025 M), sodium hydride (1.53 g. of 48% dispersion, 0.028 M) in dimethylformamide (55 ml.). The fumarate melts with decomposition at 174—176°C.

Analysis:

	C	H	N
Calculated for $C_{25}H_{36}N_2O_4$	70.06	8.47	6.54
Found	69.81	8.20	6.58

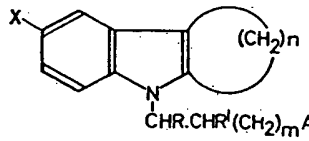
The 2,3-octamethyleneindole required as starting material in this example is prepared by the method of Buu-Hoi (J. Chem. Soc., 2882—8, *1949*) as follows: A mixture of 11.87 g. cyclodecanone and 24.9 g. phenyl-hydrazine is heated to about 100°C. until steam ceases to be evolved. The mixture is cooled, and 15 cc of glacial acetic acid saturated with dry hydrogen chloride is added cautiously. The mixture is boiled for 5 minutes and poured into water. The crude product is dissolved in benzene, washed with water, dried, and distilled. A viscous oil distilling at 152° C/0.3 mm Hg is recrystallized from alcohol and water. m.p., 92—93°C.

Analysis:

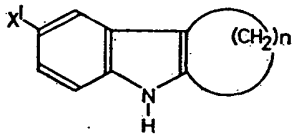
	C	H	N
Calculated for $C_{16}H_{21}N$	84.53	9.30	6.16
Found	84.25	9.31	6.13

WHAT WE CLAIM IS:—

1. Process for producing an N-substituted 2,3-polymethyleneindole having the fromula



in which X is hydrogen, halogen, nitro, amino, or methyl, R is hydrogen or phenyl, R^1 is hydrogen or methyl, Am is amino, lower alkyl-amino, di(lower)alkylamino, di(hydroxy lower alkyl)amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino and N-hydroxy lower alkyl piperazino, m is 0 or an integer of from 1 to 4, and n is an integer of from 5 to 13, which comprises reacting a 2,3-polymethyleneindole having the formula



in which X^1 is hydrogen, halogen, nitro, or methyl, and n is an integer from 5 to 13, with a reagent capable of substituting on the indole nitrogen atom a substituent having the formula

$$—W—CHR^1(CH_2)_mY$$

where W is methylene, benzylidene, or —C:O.O—, R^1 is hydrogen or methyl, m is 0 or an integer of from 1 to 4, and Y is a

carboxylic acid radical, a carboxylic ester radical, a nitrole radical, a hydroxy radical, chlorine, bromine, iodine, an alkylsulfonoxy radical, an arylsulfonoxy radical, or amino, lower alkylamino, di(lower)alkylamino, hydroxy(lower)alkylamino, di(hydroxy lower alkyl) amino piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N-hydroxy lower alkyl piperazino, heating where W is —COO and, where Y is a carboxylic acid radical, a carboxylic ester radical, a nitrile radical, a hydroxy radical, a halogen atom, an alkylsulfonoxy radical or an arylsulfonoxy radical, further reacting by amidating in the case where Y is halogen, alkylsulfonoxy, or arylsulfonoxy; reducing followed by halogenation of the hydroxyl group produced thereby and amidating the halogen group, or amidating and reducing where Y is a carboxylic acid radical or a carboxylic acid ester; halogenating and amidating where Y is hydroxyl, and where Y is nitrile reducing or forming the corresponding carboalkoxyalkyl compound and then reducing, halogenating and amidating or amidating and reducing to convert these radicals to an amino, lower alkylamino, di(lower)alkylamino, hydroxy-(lower)alkylamino, di(hydroxy lower alkyl)-amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino, or N-hydroxy lower alkyl piperazino, and. if desired, when the product is a primary or secondary amine further subjecting the same to N-alkylation or N-hydroxy-alkylation and, if desired, where X^1 is nitro reducing to the corresponding 5-amino compound.

2. A process as claimed in claim 1, in which m is 0 or 1.

3. A process as claimed in claim 1 or 2, in which n is an integer from 5 to 8.

4. Process as claimed in claim 1, in which the starting 2,3-polymethyleneindole is converted to one of its alkali metal salts which is then reacted by heating with a dialkylaminoalkyl halide to form the desired product.

5. Process as claimed in claim 1, in which the starting 2,3-polymethyleneindole is treated with a dialkylaminoalkyl chloroformate.

6. Process as claimed in any of claims 1 to 3 and 5 in which a product where W is —C: O.O— is heated to expel CO_2.

7. Process as claimed in any of Claims 1 to 3 in which a product where Y is halogen, alkylsulfonoxy or arylsulfonoxy is amidated with ammonia, a primary amine or a secondary amine containing not more than eight carbon atoms to form the final product.

8. Process as claimed in any of Claims 1 to 3, and 7, in which a product where Y is hydroxyl is reacted with a reagent capable of replacing hydroxyl with halogen.

9. Process as claimed in any of Claims 1 to 3, in which a product where Y is the nitrile radical is reduced to the $—CH_2NH_2$ radical.

10. Process as claimed in any of Claims 1 to 3, in which a product where Y is a carboxylic acid radical or a carboxylic acid ester is amidated with ammonia, a primary amine or a secondary amine containing not more than eight carbon atoms to form a carboxamide which is then reduced to the final product.

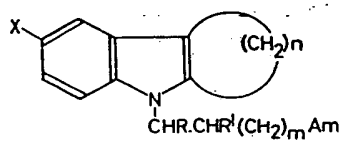
11. Process as claimed in any of Claims 1 to 3, in which a product where Y is a carboxylic acid radical or a carboxylic acid ester is reduced to a $—CH_2OH$ derivative, which is converted to a $—CH_2$-halogen group and the latter, to a $—CH_2$-amino group.

12. Process according to any of the foregoing claims, in which a product where X^1 is nitro is reduced to form the corresponding amino compound.

13. Process for the production of N-substituted - 2,3 - polymethyleneindoles having the formula defined in claim 1 substantially as hereinbefore described with reference to any of the Examples.

14. An indole whenever produced by the process of any of Claims 1—3.

15. A compound having the formula



where X is hydrogen, halogen, nitro, amino, or methyl, R is hydrogen or phenyl, R^1 is hydrogen or methyl, n is an integer of from 5 to 13, m is 0 or an integer of from 1 to 4, and Am is amino, lower alkylamino, di(lower)-alkylamino, hydroxy(lower)alkylamino, di-(hydroxy lower alkyl)amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N-hydroxy lower alkyl piperazino.

16. A compound as claimed in claim 15, in which m is 0 or 1.

17. A compound as claimed in claim 15, or 16, in which n is an integer of from 5 to 8.

18. 1 - (3 - Dimethylaminopropyl) - 2,3-hexamethyleneindole.

19. 1 - (3 - Dimethylaminopropyl) - 2,3-pentamethyleneindole.

20. 1 - (3 - Methylaminopropyl) - 2,3-hexamethyleneindole.

21. 5 - Amino - 1 - (3 - dimethylaminopropyl) - 2,3 - pentamethyleneindole.

22. 1 - (2 - Dimethylaminoethyl) - 2,3-hexamethyleneindole.

23. 1 - (3 - Dimethylaminopropyl) - 2,3-octamethyleneindole.

24. 1 - (2 - Piperidinoethyl) - 2,3 - pentamethyleneindole.

25. 1 - (3 - Dimethylaminopropyl) - 2,3-tridecamethyleneindole.

26. A compound having the formula given in claim 15 substantially as hereinbefore described with reference to and as illustrated in any of Examples 1 to 5 and 8 to 22.

27. A compound having the general formula defined in claim 15 substantially as hereinbefore described with reference to Example 6 or 7.

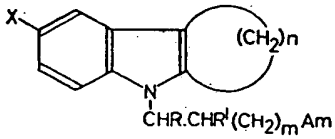
28. A salt of a compound as claimed in any of claims 14 to 26 with a pharmaceutically acceptable acid.

29. A salt of a compound as claimed in claim 27 with a pharmaceutically acceptable acid.

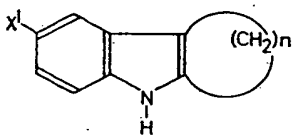
30. A therapeutic composition containing any one of the products of claims 14 to 26 and 28, and a pharmaceutically acceptable carrier.

31. A therapeutic composition containing a product of claim 27 or 29 and a pharmaceutically acceptable carrier.

32. Process for producing an N-substituted 2,3-polymethyleneindole having the formula



in which X is hydrogen, halogen, nitro, amino, N-methyl, R is hydrogen or phenyl, R^1 is hydrogen or methyl, Am is amino, lower alkylamino, di (lower) alkylamino, hydroxy (lower) alkylamino, di(hydroxy - lower alkyl) - amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino and N-(hydroxy lower alkyl)piperazino, m is 0 or an integer of from 1 to 4, and n is an integer of from 5 to 13, which comprises reacting a 2,3-polymethyleneindole having the formula



in which X^1 is hydrogen, halogen, nitro, or methyl, and n is an integer from 5 to 13, with a reagent capable of substituting on the indole nitrogen atom a substituent having the formula

$$—W—CHR^1(CH_2)_mY$$

where W is methylene, benzylidene, or —C:O.O—, R^1 is hydrogen or methyl, m is 0 or an integer of from 1 to 4, and Y is a carboxylic acid radical, a carboxylic ester radical, a nitrile radical, an hydroxy radical, chlorine, bromine, iodine, or amino, lower alkylamino, di (lower) alkylamino, hydroxy (lower) alkylamino, di(hydroxy lower alkyl) amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino or N-hydroxy lower alkyl piperazino, heating where W is —COO and, where Y is a carboxylic acid radical, carboxylic ester radical, a nitrile radical, a hydroxy radical or a halogen atom, further reacting by amidating in the case where Y is halogen; reducing followed by halogenation of the hydroxyl group produced thereby and amidation of the halogen group or amidating and reducing where Y is a carboxylic acid radical or a carboxylic acid ester; halogenating and amidating where Y is hydroxyl, and where Y is nitrile, reducing or forming the corresponding carboalkoxyalkyl compound and then reducing, halogenating or amidating or amidating and reducing to convert these radicals to an amino, lower alkylamino, di (lower) alkylamino, hydroxy (lower) alkylamino, di (hydroxy lower alkyl) amino, piperidino, morpholino, pyrrolidino, piperazino, N-lower alkyl piperazino, a N-hydroxy lower alkyl piperazino, and, if desired, when the product is a primary or secondary amine further subjecting the same to N-alkylation or N-hydroxyalkylation and, if desired, reducing the compound where X^1 is nitro to the corresponding 5-amino compound.

33. Process as claimed in claim 32 in which m is 0 or 1.

34. Process as claimed in claim 32 or 33 in which n is an integer from 5 to 8.

35. Process as claimed in claim 32 substantially as hereinbefore described with reference to any of Examples 1 to 5 and 8 to 22.

36. An indole whenever prepared by a process as claimed in any of claims 32 to 35.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool, 1,
Chartered Patent Agents.

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ERRATA

SPECIFICATION No. 1,013,908 No. 2

Page 3, line 60, *after* "1" *insert* "hyphen"
Page 5, line 69, *for* "1,3-" *read* "2,3-"
Page 8, line 71, *for* "(5.4 g.," *read* "(4.5 g.,"
Page 9, line 66, *for* "fromula" *read* "formula"
Page 10, line 89, formula, *after* "CHRCHR'" *insert* "hyphen"

THE PATENT OFFICE
30th September 1968

CORRECTION OF CLERICAL ERRORS

SPECIFICATION NO. 1,013,908

AMENDMENT NO. 1

The following correction is in accordance with the Decision of the Superintendent Examiner, acting for the Comptroller-General dated the fifteenth day of June 1966.

Page 2, line 67, *after* "reducing" *insert* comma

Page 4, line 34, *for* "225C" *read* "225°C"

Page 4, line 36, the three columns of figures on lines 37 and 38 should be headed "C, H, N"

Page 4, line 42, *delete* opening bracket *before* "31"

Page 7, line 56, *for* ".3:" *read* ".3mm:"

Page 9, line 10, *for* "dimethylformamide" *read* "dimethylformamide)."

Page 9, line 74, *for* "and" *read* "or"

Page 10, line 7, *after* "amino" *insert* comma

Page 11, line 23, *for* "and" *read* "or"

Page 11, line 57, *for* "halogenating or" *read* "halogenating and"

ERRATA

SPECIFICATION NO. 1,013,908

AMENDMENT NO. 1

Page 2, line 13, *for* "alkylsulfonyloxy" *read* "alkylsulfonoxy"

Page 2, lines 14 and 15, *for* "di (hydroxyamino" *read* "di (lower) alkylamino"

Page 5, line 49 *for* "Dimethylominapropyl" *read* "Dimethylaminopropyl"

Page 7, lines 2, 3 and 4, the expression "(Base)" on line 3 should occur after "F" on line 2, and "Found" on line 4 should occur in place of (Base) on line 3"

Page 9, line 71 *after* "di (lower) alkylamino" *insert* "hydroxy (lower) alkylamino"

Page 10, line 2 *for* "nitrole" *read* "nitrile"

Page 10, line 87 *for* "1-3" *read* "1-13"

Page 11, line 18 *for* "N-methyl" *read* "or methyl"

THE PATENT OFFICE,
16th September, 1966

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